

Letter to the Editor

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Ouabain and Serum Sodium

To the Editor:

Sodium-dependent mechanisms play a role in the pathogenesis of hypertension. He et al recently demonstrated that in normotensive and hypertensive subjects an acute reduction in salt intake, from 350 to 10 mmol/d for 5 days, was associated with a decline in serum sodium by ≈ 3 mmol/L.¹ Conversely, a progressive increase in salt intake from 10 to 250 mmol/d by a daily amount of 50 mmol caused an increase in serum sodium in normotensive subjects, but not hypertensive patients.¹ These investigators speculated that small changes in serum sodium might directly affect the hypothalamic control of blood pressure through the local pituitary renin-angiotensin system.¹

Ouabain is a steroid hormone, which is released from the hypothalamus and the adrenal gland. It is implicated in sodium homeostasis and exerts direct actions on the vasculature, the heart,² and tubular sodium reabsorption.³ In individuals randomly recruited from a Flemish population, blood pressure increased by 2.2 mm Hg systolic and 1.4 mm Hg diastolic for each 50-mmol/d increment in urinary sodium excretion when the plasma ouabain concentration was below the median (140 pmol/L).⁴ No association between blood pressure and urinary sodium was found when plasma ouabain exceeded the median.⁴

In the same population,⁴ we tried to reproduce He's observations in 369 subjects not using treatment with diuretics. Blood pressure was the average of 5 consecutive readings obtained at each of 2 home visits 4 to 6 weeks apart. The study sample included 48.0% men, 30.9% current smokers, and 25.5% hypertensive patients. Mean age was 39.8 ± 16.7 (SD) years. Mean values for systolic/diastolic blood pressure, serum sodium, and the 24-hour urinary sodium excretion were $123 \pm 15/77 \pm 11$ mm Hg, 141.6 ± 2.5 mmol/L, and 192 ± 61 (range, 24 to 391) mmol/d, respectively. The geometric mean concentration of plasma ouabain was 145 (95% confidence interval, 138 to 148) pmol/L. With adjustment for sex, age, body mass index, and current smoking, serum sodium did not increase with sodium excretion (partial $r=0.01$, $P=0.88$). However, with similar adjustments, we found an independent and positive relation between the serum concentrations of sodium and ouabain with a partial correlation coefficient of 0.12 (95% confidence interval, 0.02 to 0.22, $P=0.03$). In a sensitivity analysis only including 334 untreated subjects, the partial correlation coefficient was 0.11 (95% confidence interval, 0.00 to 0.22, $P=0.06$). This relation was stronger in men than in women ($r=0.18$ versus $r=0.03$, respectively; $P<0.001$).

In conclusion, our observational study in Flemish subjects free from antihypertensive therapy did not confirm that serum sodium increased with urinary sodium excretion. However, in line with the perspectives of He's recent article,¹ we noticed that the serum sodium concentration, which is a tightly regulated variable, is positively and independently correlated with plasma ouabain, a hypothalamic and adrenal hormone. Further research should assess whether this association is direct, whether it is mediated via extracellular volume or endocrine factors, and whether it is different in women and men.

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Response: Ouabain and Serum Sodium

We are grateful to Gasowski et al for raising an interesting point on plasma sodium and ouabain. They found a significant association between these 2 variables in a cross-sectional study of 369 individuals.¹ This finding, in conjunction with those from experimental studies in rats,² which showed that the increase in blood pressure induced by an increase in cerebral spinal fluid sodium was secondary to an increase in ouabain content in the hypothalamus, and could be prevented by the intracerebroventricular administration of Fab fragments, which bound ouabain, suggests that the effect of plasma sodium on blood pressure may be, in part, through increasing ouabain concentration both in plasma and in the hypothalamus.

In our article,³ we looked at 3 types of studies of changing salt intake and demonstrated that when salt intake is increased or decreased, there is a parallel change in plasma sodium. Small changes in plasma sodium alter extracellular volume, which may influence blood pressure. At the same time, changes in plasma sodium may also affect blood pressure directly. It is an important attempt that Gasowski et al tried to reproduce these findings using the data of their cross-sectional study, presumably trying to answer an important question of whether habitual salt intake is related to plasma sodium. However, addressing this question would need careful measurements of both plasma and urinary sodium in a large number of individuals under controlled conditions because of a large day-to-day variation in salt intake. In addition, the concentration of sodium in plasma is closely and rapidly controlled by the movement of fluid between the intracellular and extracellular compartment, changes in sodium excretion, and by the activity of thirst center,⁴ which, in rat, is influenced by changes in plasma sodium of $<1\%$.⁵ Such small

and potent changes in plasma sodium are technically difficult to detect. The methods used in the cross-sectional study by Gasowski et al made it even more difficult to look at the relationship between salt intake and plasma sodium. First, only one 24-hour urine collection was made, which certainly does not represent an individual's habitual salt intake. Furthermore, blood sample was taken several days after the urine collection ("usually within 2 weeks of urine collection" as stated in the original publication¹). It is therefore not surprising that they could not reproduce our findings from well-controlled clinical trials.

Gasowski et al also misquoted our results by stating that "a progressive increase in salt intake from 10 to 250 mmol/d by a daily amount of 50 mmol caused an increase in plasma sodium in normotensive subjects, but not hypertensive patients." In our article, we clearly indicated that only normotensive individuals were studied using this protocol (ie, progressive increase in salt intake). However, our acute salt reduction studies in which both hypertensive subjects and normotensive subjects were studied, showed a similar decrease in plasma sodium when salt intake was reduced from ≈ 350 to 10 mmol/d. Therefore, there is no

reason to believe that hypertensive individuals would not show an increase in plasma sodium with increasing salt intake.

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